Review article

Multiple sclerosis: its epidemiological, genetic, and health care impact

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Multiple sclerosis (MS) is a disease of relatively low incidence in the United Kingdom. Because of its long clinical course, however, its prevalence is moderately high and it makes a considerable impact on individuals, families, and on the health and social services. The inclusion in this review of the epidemiology, genetics, and health care of MS is intended to stress the inter-relationship between these three aspects of the disorder.

MS is a demyelinating disease of the central nervous system. As a chronic disease, it offers a number of challenges to the epidemiologist. Firstly, although there are specific diagnostic criteria (see below), making a definitive diagnosis of MS is frequently difficult. Secondly, at any one time an unknown number of people who have symptoms of MS and who will subsequently be labelled as having the disease have yet to be diagnosed. Thirdly, its aetiology and the factors which determine the course of the disease are largely unknown. Lastly, new investigative techniques (particularly nuclear magnetic resonance imaging (MRI)) have shown central nervous system (CNS) lesions, characteristic of those found in MS in people who are free from symptoms. MRI may have important implications for monitoring disease activity in individual patients.[1]

Prevalence and incidence

Several studies of UK populations have provided data on the prevalence of MS.[2-7] These, as examples of the range of prevalence estimates, are summarised in the table. They have used a variety of methods for case ascertainment and different classification criteria. They are also spread over a number of years.

Estimates of prevalence, summarised by Compston and Sadovnick[8] range from 99/100 000 in the south of England to 178/100 000 in north east Scotland. This north-south gradient in prevalence observed in the United Kingdom is reflected, to a large extent, in other countries of the northern hemisphere. Most of the small number of studies that have been carried out support the notion that the incidence of MS is low at the equator and increases towards the poles. Information on the prevalence of MS throughout the world has not advanced significantly since the publication of Acheson's 1977 review.[9] A map of the world showing the distribution of MS is reproduced from Acheson's report (fig 1).

The most recent estimate of incidence for the UK is that of Mumford *et al*[7] for the population of Cambridgeshire. Their overall estimate was 5·94/100 000/year. Studies of the

Examples of population based studies of multiple sclerosis (MS) in the United Kingdom

Authors and date of study	*Population*	*Ascertainment methods*	*Diagnostic criteria*	*Crude prevalence ($\times 10^{-5}$) (95% CI)*	*Incidence ($\times 10^{-5} \times y^{-1}$) (95% CI)*	*Comments*
Pozkanzer *et al*[2] 1958	Northumberland & Co Durham	GP records, hospital records	Clinical	50 (45, 50)	Not available	Said to be minimum figure
Phadke & Downie[3] 1970, 1973, 1980	Grampian Region	Hospital records, neurology dept records, MS Society records, community nurses	Modified Allison and Millar[55]	1970 - 127 (116, 138) 1973 - 144 (133, 155) 1980 - 178 (166, 190)	1959-61 - 4·6 1968-70 - 6·0 1977-80 - 7·2	Suggests increasing prevalence and incidence
Swingler & Compston[4] 1985	South Glamorgan	Neurology inpatients, hospital records, general practice records, MS Society, community nurses & physios	Poser *et al*[10]	117 (106, 128) - all cases 101 (90, 111) - definite or probable 16 (12, 21) - suspected	1947-49 - 3·3 (1·9, 4·6) 1965-67 - 5·3 (4·0, 6·6) 1983-84 - 8·9 (6·7, 11·0)	Suggests increasing incidence (better ascertainment acknowledged)
Roberts *et al*[5] 1987	Southampton & South West Hampshire Health Authority	GP records, HAA* data, MS Society records, ARMS†, consultant neurologists, dependent disabled register, neurology department, young disabled unit	Allison & Millar[55] Poser *et al*[10]	99 (89, 109) - all cases 92 (83, 101) - probable 7 (4, 10) - possible 95 (88, 107) - definite or probable 4 (2, 6) - suspected	Not available	Compares breakdown of MS cases by Poser and Allison & Millar criteria
Lockyer *et al*[5] 1988	Rural Suffolk	GP records, hospital records, social services, community nurses, MS Society	Allison & Millar[55] Poser *et al*[10]	153 (109, 196)	Not available	Small sample size acknowledged
Mumford *et al*[7] 1989-91	Cambridge Health District	Hospital records, GP records, nursing homes, MS Society	Allison & Millar[55] Poser *et al*[10]	130 (117, 143) - all cases 107 (95, 119) - probable 23 (17, 28) - possible 110 (98, 122) - definite or probable 19 (14, 25) - suspected	6·0 (4·0, 10·0)	Compares breakdown of MS cases by Poser and Allison & Millar criteria

* Hospital Activity Analysis, † Action for Research in Multiple Sclerosis.

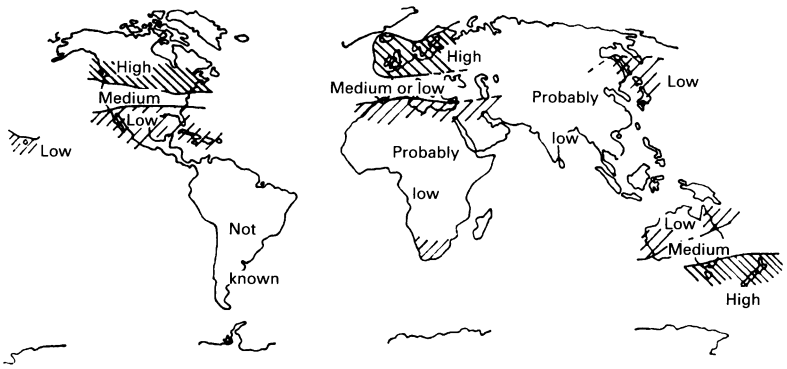

Figure 1 Map of the world showing the distribution of multiple sclerosis reprinted by permission of the British Medical Bulletin.[9]

occurrence of MS are difficult to interpret for the following reasons:

(1) They have been carried out at different times. If the prevalence of MS is rising for any reason (longer survival, better ascertainment, rising incidence, or a combination of these factors) then prevalence and incidence data gathered at different times cannot be compared directly.
(2) Different methods of case ascertainment have been used.
(3) Few studies have used the currently advocated classification criteria of Poser *et al*[10] since many of them were carried out before these were published. This reduces their value and comparability.
(4) Although most studies have attempted complete ascertainment, there has been little use of the well documented "capture–recapture" (or ascertainment intersection) method for estimating the degree of under ascertainment.[11–14] This method is currently being advocated for epidemiological surveys so that corrections for any degree of under ascertainment can be made.
(5) Although several of the cross sectional studies of MS listed above have provided age and sex specific prevalence data,[7] for example, some have not. This makes standardisation, to take account of differences in age, gender, and ethnic make up of populations, impossible.

Migrant studies

Following Dean's work in South Africa[15] a number of studies of immigrant groups have been published. Dean could find no cases among the indigenous Bantu and very few cases among Coloured (mixed race) and Asian populations. It is not clear to what extent differential access to health care contributed to this finding but it is more than likely that MS was genuinely very uncommon in those groups at that time. The crude, age specific, and standardised prevalence estimates for English speakers born in South Africa were higher than estimates for those speaking Afrikaans (crude prevalence 12·7/100 000 compared with 3·6/100 000). Those who had themselves migrated from the UK were highest of all (40·9/100 000) with those from elsewhere in Europe lower (32·3/100 000), though not significantly so.

A further study in South Africa by the same author[16] took into account age at migration. Subjects who had migrated when younger than 15 had lower than expected rates while those who had migrated at ages of 16 or above had rates equal to or greater than expected. This suggested that an environmental exposure encountered in the migrant's home country before the age of 16 played a part in MS aetiology. Later work[17] has supported this notion. The exact nature of this exposure has not been determined but a number have been postulated including an unusual (genetically determined) reaction to an ubiquitous or very common agent such as the measles virus.[8]

Familial aggregation

There is evidence of familial clustering in MS. Its frequency among relatives of affected probands is between 15 and 40 times higher than in relatives of unaffected probands.[18] Sadovnick *et al*[19] also calculated sex specific absolute risks, adjusted for age. In relatives of male probands (fig 2), there was a decreasing gradient of risk with increasing family distance (from first degree to third degree kinships). Since third degree kinships, on average, share fewer of their alleles than first degree kinships, this is also evidence

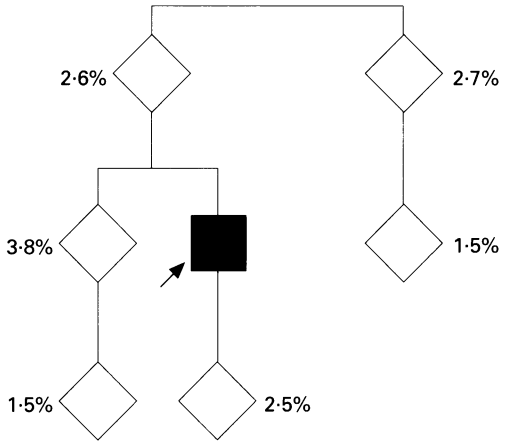

Figure 2 Frequency of multiple sclerosis in relatives of male probands.

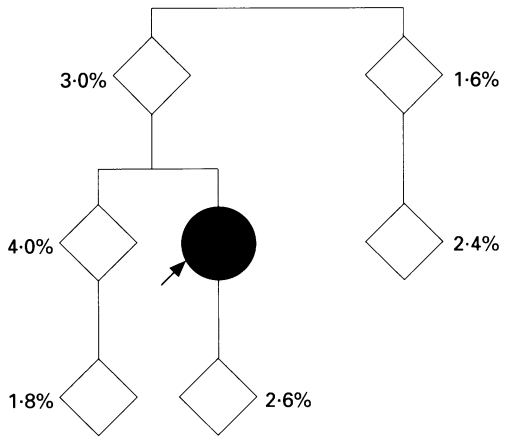

Figure 3 Frequency of multiple sclerosis in relatives of female probands.

for a genetic component to disease predisposition.[20] This trend of decreasing risk with increasing family distance is not as clear cut in relatives of female probands (fig 3).

Twin studies

There are few epidemiological studies of concordance of MS in twins. Those that have been published indicate that concordance in monozygotic twins lies between 25% and 30% in comparison to 2%–5% in dizygotic twins.[21] This is further evidence that environmental factors must play a role in disease predisposition.

Population allele associations

Genetic susceptibility to MS has been linked to genes encoded within the HLA region.[8] Many studies have compared the frequency of HLA-DR alleles in MS patients and control populations. In white subjects there is a strong association with HLA-DR2 (now HLA-DR15) (relative risk (RR) = 2–4). Interesting geographical and ethnic variations exist. In Sardinia, for example, where there is a high prevalence of disease, MS is more strongly associated with HLA-DR4 (RR = 2·5).[22] In Japan, the main association is with HLA-DR13. A detailed review of population HLA-DR associations is provided by Tiwari and Terasaki.[23]

Evidence for the involvement of other alleles is controversial. A Norwegian study[24] reported that HLA-DP alleles conferred additional susceptibility to MS but this has not been shown in other populations.[25,26] Other genes such as T cell receptors may also play a role in disease predisposition.[27]

Mode of inheritance of HLA-DR2 related susceptibility

Two analytical methods have been used to investigate the possible mode of inheritance of the HLA-DR2 related susceptibility to MS. The first is based on parental haplotype sharing in affected sib-pairs. The second is based on the genotypic distribution of probands.

AFFECTED SIB-PAIR HAPLOTYPE SHARING

This is a common method used to detect genetic linkage between a disease and a marker locus.[28,29] A key requirement of this method is that parents carry four unique marker haplotypes so that inheritance can be traced unambiguously to their offspring.

Under the assumption of no association between the disease and the marker locus, affected sibs would be expected to share 2, 1, or 0 parental haplotypes in a ratio of 1:2:1. Any deviation towards greater haplotype sharing (1 or 2) indicates the presence of an HLA-linked susceptibility allele. The affected sib method has been extended by theoretical studies to examine the mode of inheritance of disease susceptibility alleles once linkage has been established.[30–32] An excess of two haplotypes shared indicates recessive inheritance; an excess of one favours dominant inheritance.

The accumulated data of Payami *et al*[33] showed that affected MS sibs shared 2, 1, and 0 parental HLA haplotypes in a ratio of 6:3:1, which was significantly different from random expectations (1:2:1). These data, contrary to the findings of others,[34–38] suggested a recessive mode of inheritance. These discrepancies may be the result of genetic heterogeneity within MS.[33]

ANTIGEN GENOTYPE FREQUENCY AMONG PROBANDS (AGFAP)

A second source of information regarding mode of inheritance of HLA associated diseases is the AGFAP[39] method of Thomson. The AGFAP method uses the genotype frequencies of the marker allele (in this case HLA-DR2) in the probands. If a disease is inherited recessively, this implies a high proportion of individuals homozygous for the antigen of interest. In contrast, for a dominantly inherited disease, most probands will be heterozygotes.

Using the AGFAP method, Thomson[40] examined the data of Stewart *et al*[41] in which HLA-DR2 genotypic status was known. From 60 MS probands, 3 were homozygous for HLA-DR2, 37 were heterozygous, and 20 had a genotype not containing HLA-DR2. These results rejected a recessive hypothesis ($\chi^2 = 7{\cdot}6$, $p < 0{\cdot}05$) with expectations for the genotype classes DR2/DR2, DR2/DRX, X/X (where X = any allele other than DR2) of 4·9, 35·1 and 20·0 respectively. In contrast, the observed distribution was in close agreement with the dominant hypothesis ($\chi^2 = 0{\cdot}3$, p = ns) with expectations of 10·7, 29·3, and 20·0 for the three respective genotypic classes.

The mode of inheritance of HLA-linked MS remains unresolved.[42] Since the HLA locus does not account for all of the genetic susceptibility to MS,[43] this provides evidence for additional familial determinants which may be genetic or environmental in their origins.

Impairment, disability, and handicap

The consequence of the demyelinating process in MS is a loss of neuronal integrity and impairment of axonal function. The location, number, and size of the demyelinated plaques are determinants of the severity of the disease. However, the sudden onset of symptoms and striking capacity for remission together with the frequent lack of correlation between anatomical lesions and the degree of impairment make prognosis difficult to assess. Tissue damage may lead to impairments in any aspect of brain and spinal cord activity ranging from abnormal signs to complete loss of function.

Assessment of impairment, disability, and handicap

Characteristically, MS affects several different areas of the central nervous system and its manifestations are manifold. Evaluation scales therefore attempt to combine signs of dys-

function in different functional and anatomical systems.[44-48] Lack of generally accepted laboratory, imaging, or electrophysiological measures of disease activity has confined assessment of response to drug therapy and prognostic studies to the change in levels of impairment determined by neurological examination.

Although no ideal system has yet been devised (see Willoughby and Paty[50] for a critical review of scales for rating impairment) the most commonly used method for assessing impairment is that of Kurtzke.[49] In an attempt at standardisation, this system has been incorporated by the International Federation of Multiple Sclerosis Societies (IFMSS) into its Minimal Record of Disability for MS (MRD).[51] The MRD maps onto the WHO three tier dysfunction classification of impairment, disability, and handicap.[52]

Impairment is assessed by ascribing a score to each of eight items (cerebellar, brainstem, mental function, pyramidal, sensory, bowel and bladder, visual function, and spasticity) on the Kurtzke functional scale. The Kurtzke expanded disability status scale (EDSS) incorporates these weighted scores into a single measure of impairment ranging from zero (normal neurological examination) to 10 (death due to MS) in half-point increments. Disability is assessed by the incapacity status scale, a 16 item inventory of activities of daily living. Finally the environmental status scale, by examining factors such as employment, financial, and social activity, addresses the degree of handicap experienced by an individual as a result of neurological impairment.

The prevalence of disability (impairment)

Because of its relapsing/remitting or progressive nature the level of disability experienced by an individual varies over time. There is growing awareness that, for effective planning and provision of services, the prevalence, needs, and prognosis of people with MS require quantification in population based cohorts.[53,54] Several studies have examined morbidity within geographically defined populations but differences in case ascertainment, disability grading scales, and diagnostic criteria[10,55,56] make comparability difficult. The published reports in this area have been extensively reviewed by others.[57]

Studies using the Kurtzke classification commonly show a bimodal distribution in the prevalence of dysfunction with peaks in both the mild and the severe ranges.[50,53,58] Between 30% and 50% of cases have impairment severe enough to require walking aids or a wheelchair (EDSS 6 or greater)[53,54,58] while only 25% walked with normal gait.[53] One recent MRD study in the US,[53] claiming virtual 100% ascertainment of MS cases, reported a third of patients as having marked paraparesis and a quarter of patients needing catheterisation for bladder dysfunction.

While the most common finding on neurological assessment was a defect in visual function (83%), the proportion with severe visual impairment or total loss of vision was 9%. In this series 4% of the patients reported severe decreases in mentation or dementia and 8% were in institutions. Unemployment among MS patients is approximately 50%[53,59] but 75% of cases were able to maintain their financial status.[53]

A variety of factors have been linked to the prediction of subsequent disability and survival. Favourable prognostic criteria include an age of onset below 40 years; presentation with optic neuritis without limb weakness; long interval on first remission without a progressive course and an isolated sensory disturbance of spinal cord origin.[60-66] The level of clinical disability after five years of illness has been suggested as the most reliable predictor of long term outcome currently available.[61,62]

About a third of patients can expect a benign course with minimal disability after 10–15 years of onset[54,62,63,68] and up to 14% after 25 years. Longitudinal studies suggest an annual mortality rate among MS sufferers of between 1% and 4%.[63,69,70,71] Two thirds of these deaths are MS related.[62,63]

Health care and social support

Despite the fact that MS is a common cause of non-traumatic disability among young adults, little research is available on how best to deliver high quality health and social care. Important questions are: (1) What are the aims of care? (2) Under what circumstances is specialist intervention (for example by a neurologist or physiotherapist) appropriate? (3) To what extent are needs met by the current pattern of service provision? and (4) How can the effectiveness of future service developments be monitored?

Aims of treatment

A number of authors from different disciplines have described their own understanding of ideal care – neurologists,[71,72] social workers,[73] and social scientists.[74] Clinicians tend to emphasise symptom control[75] whereas nurses focus on the encouragement of self esteem and coping strategies.[76,77] A common belief is that high quality care must be tailored to the needs of each individual.[78,79] This creates challenges for the evaluation of overall patterns of service delivery.

Role of specialist intervention

The ideal study would compare the outcome, efficiency, and acceptability of a programme of care including specialist intervention with that of a programme without it. In practice, effects as judged by before and after measurements are reported without any control group. Some of the specialist interventions which have been evaluated in this way include early diagnostic investigation,[78] group psychotherapy,[79] prolonged inpatient physiotherapy,[80,81] and the teaching of intermittent self catheterisation.[82] None of these reports describes the costs of these interventions or identifies a particular

subgroup of patients who are most likely to benefit.

Drug therapy to prevent or control exacerbations also involves specialist care. Hyperbaric oxygen,[83] intravenous gammaglobulin,[84] and immunosuppression[85] have all been shown to be ineffective. However, the use of interferon beta-1b, produced by recombinant-DNA techniques, has been shown to reduce the frequency and severity of relapses.[86] If its effectiveness is confirmed in routine clinical practice, this will have important implications for the overall costs of MS care.[87 88]

Adequacy of present service provision

There are only two published surveys in the UK and these date from 1983[89] and 1977,[90] so their findings are of doubtful relevance today. Their findings of inadequate help with retraining for employment and with transport are reproduced by similar studies from Denmark[91] and Washington, USA.[92] The only area of over provision of care suggested by the more recent of the UK studies[89] was the frequency of contact with a consultant neurologist – 60% of respondents being seen at least once every six months. This was considered unnecessarily often in view of the lack of therapeutic options, but others have suggested that repeated scheduled examinations are important.[71]

The health status of carers[77] and of the families of MS patients have been reported in specific case series, using named instruments, but these have not been translated into health care needs. In contrast to the findings of Rodriguez *et al*,[53] the average economic status of such households was found to be poor.[93 94]

Measurement of effectiveness

As explained above, the most commonly used disease-specific measure for evaluation of drug therapy is the EDSS of Kurtzke.[49] Other reported specific instruments are the MS stressor scale and the Jalowiec coping scale.[95] These can be used to evaluate patterns of health care delivery but their validity is unproved. Basic generic scales such as one of the medical outcomes study batteries[96] and the incapacity status scale[97] have also been used, but only in individual studies. None of these instruments is suitable for routine evaluation of MS care as they are time consuming to administer. Mortality rates have the advantage of a definite end point, but, on their own, they say little about the impact of health care interventions. MS patients have a life expectancy six to seven years less than the general population.[98]

Suggested priorities for future research

Community based surveys have revealed unmet needs and suggested interventions to address these, such as dedicated assessment clinics and specialised social workers. Before the cost effectiveness of these interventions can be measured, a generic scale for health related quality of life needs to be found which correlates with patient and carer assessment and disease specific scales. Without such a scale, alternative patterns of service delivery could still be compared, for instance those based on primary care compared with those focussed on secondary care. The possible introduction of relatively expensive bioengineered products, such as interferon beta-1b, will increase the need to investigate the cost effectiveness of simpler interventions such as physiotherapy and carer support.

The British Society of Rehabilitation Medicine,[99] while emphasising that "a search for the cause and pathogenesis of MS is a first priority in research", recognises the need for "longitudinal surveys in which quantitative medical, functional and social information are collected" in order "to understand the processes by which impairment leads to disability and handicap" and to "identify ways in which the quality of life of those who have it can be protected". The Nuffield Institute for Health, in collaboration with the Department of Neurology, St James' University Hospital, Leeds, is currently conducting a population based study of MS in West Yorkshire which will address some of these issues.

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